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Innovative Processes for Validating Diagnostic Tests for Rare Biomarkers or Indications

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Companion Diagnostic (CDx) and Drug Co-Development Paradigm

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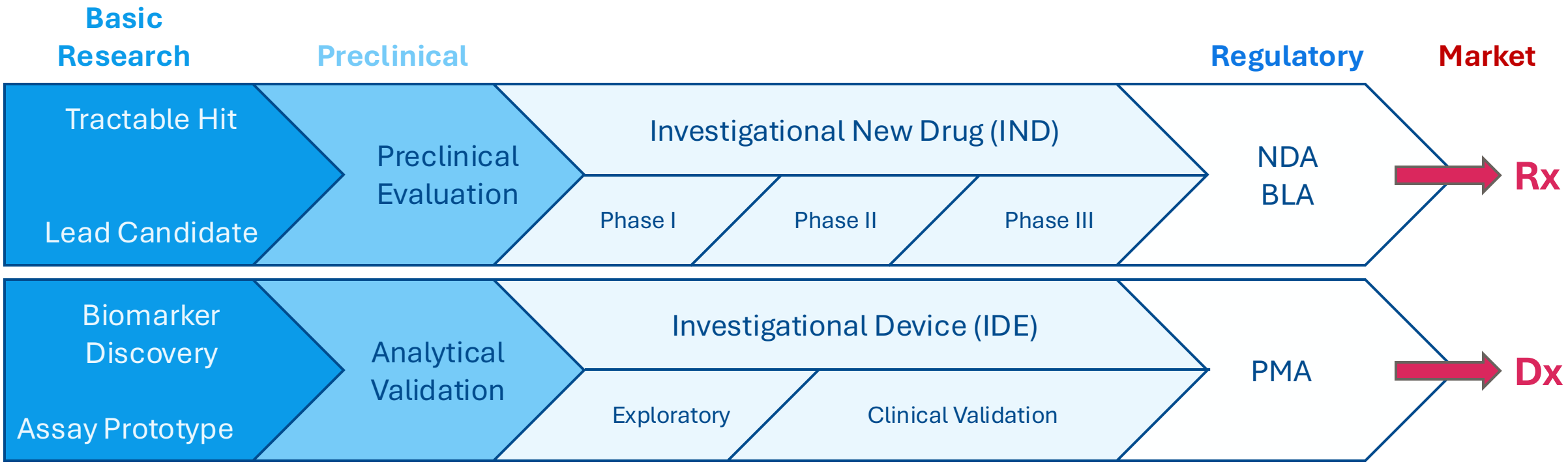

Source: FDA

For rare biomarkers or indications, clinical samples are often limited which makes test validation challenging, particularly when drug development timelines may be compressed.

Rare Biomarkers Working Group

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Objectives:

- Identify situations where regulatory flexibilities would be appropriate to help facilitate validation of companion diagnostics (CDx) for rare biomarkers and indications in oncology.
- Given that samples are rare in these scenarios, develop approaches for leveraging alternative sample sources or data to support validation strategies.
- Outline a framework for capturing key information to support the proposed validation strategy, particularly when using alternative samples, to enable productive conversations with FDA and ensure clarity in premarket submissions.

Defining Rare Biomarkers and Indications

- Estimated biomarker prevalence of 1% or lower (in the population of patients with that specific cancer type in the U.S.)
- For rare cancer types with an estimated total prevalence of 1% or lower (in the overall population of patients with cancer in the U.S.)
- Other data and information are considered for determining regulatory flexibility

Ultimately, there are limited clinical samples in these scenarios

Approach to CDx Validation

Establishment of specific performance characteristics for the test

Analytical validation

- Ensure tests are accurate, precise, specific, and reliable
- Does not require clinical outcomes

Clinical validation

- The accuracy with which the test identifies the patients for whom the therapy is safe and effective
- Requires clinical outcomes

For rare biomarkers, consider alternative sample sources for performing these analyses

Use of Alternative Data Sources for Validation

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Data or Sample Type Category	Use in Validation
Clinical Trial Samples	Prioritize for clinical validation (e.g., bridging studies)
Representative Clinical Approaches	Analytical validation, can include generalized conclusions for variants in similar genomic contexts (e.g. different cancer or sample type)
Real-World Evidence	Clinical validation, often in the post-market
Procured Human Specimens	Analytical validation (e.g., LOD, accuracy, precision, and other key analytical studies related to the specimen (e.g., stability))
Cell Lines	Analytical validation (e.g., interference, reagent stability, input of intermediate steps, guard banding)
Contrived Samples	Analytical validation (e.g., linearity, stability, reproducibility, interfering substances, etc.)
In Silico Datasets	Validating bioinformatics pipeline and other informatics components

Tools for Discussing Validation Strategy with FDA

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A “snapshot” providing justification for the rareness of the biomarker and an approach to validation studies can support improved communication between sponsors and FDA

Category	Description
Validation Study *Describe which study you will be using the proposed samples for*	
Proposed Samples *Describe the samples and include the anticipated sample size*	
Sample Source *Describe how the samples are procured*	
Sample Justification *Describe the justification behind using these samples*	

Key Takeaways from White Paper

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- Regulatory flexibilities can aid in demonstrating a favorable benefit-risk profile for CDx for rare biomarkers and indications
- Alternative evidence sources can support clinical and analytical validation for CDx biomarker tests when specimen availability is limited
- Sponsors should provide an explanation for why samples would be limited and discuss plans for using alternative data or samples for validation with the FDA
    - Sponsors could consider using the proposed snapshot document to more effectively facilitate these discussions